REVIEW

Alterations in Carbohydrate Metabolism During Stress: A Review of the Literature

Barry A. Mizock, MD, FACP, *Chicago, Illinois*

Patients with sepsis, burn, or trauma commonly enter a hypermetabolic stress state that is associated with a number of alterations in carbohydrate metabolism. These alterations include enhanced peripheral glucose uptake and utilization, hyperlactatemia, increased glucose production, depressed glycogenesis, glucose intolerance, and insulin resistance. The hypermetabolic state is induced by the area of infection or injury as well as by organs involved in the immunologic response to stress; it generates a glycemic milieu that is directed toward satisfying an obligatory requirement for glucose as an energy substrate. This article reviews experimental and clinical data that indicate potential mechanisms for these alterations and emphasizes aspects that have relevance for the clinician.

The nomenclature of critical care medicine uses the term "stress" to describe the systemic response to severe injury or infection.[1] The stress response is manifest as a syndrome consisting of hypermetabolism (eg, increased oxygen consumption, hyperglycemia, hyperlactatemia, protein catabolism), a hyperdynamic cardiovascular state, and clinical manifestations of fever or hypothermia, tachycardia, tachypnea, and leukocytosis.[2] The intensity of the stress response peaks several days after the initial insult and diminishes during recovery.[3] A prolonged response may occur in patients who have persistent tissue hypoperfusion or an unresolved focus of injury or infection; that in turn predisposes them to the development of progressive metabolic dysregulation and organ failure.[3]

The etiology of hypermetabolism during stress is unclear. Stoner[4] has portrayed it as a dichotomy of "push versus pull"; that is, metabolism may either be "pushed" to higher levels by the existing neurohormonal milieu—similar to what is observed in hyperthyroidism—or "pulled" by the metabolic demands of the area of infection or injury. Wilmore,[5] using data obtained from burns, proposed that the wound functions as an "organ of repair" that stimulates hypermetabolism through the production of neuroendocrine and cytokine mediators to satisfy the demands of the reparative process.

From the Division of Critical Care Medicine and the Department of Medicine, the Chicago Medical School and Cook County Hospital, Chicago, Illinois.

Requests for reprints should be addressed to Barry A. Mizock, MD, Department of Medicine, Cook County Hospital, 1835 West Harrison Street, Chicago, Illinois 60612.

Manuscript submitted July 1, 1994 and accepted September 2, 1994.

Acute infection or injury induces a number of alterations in carbohydrate metabolism. They include enhanced peripheral glucose uptake and utilization, hyperlactatemia, increased glucose production, depressed glycogenesis, glucose intolerance, and insulin resistance. The discussion that follows will present animal and human data that suggest potential mechanisms for these alterations. In addition, features that have particular relevance for the clinician will be highlighted.

ENHANCED PERIPHERAL GLUCOSE UPTAKE

Severe injury or infection is associated with enhanced cellular uptake of glucose.[6,7] Recent research has provided insights into potential mechanisms underlying this process. The cell membrane has a hydrophobic interior that renders it impermeable to small polar molecules such as glucose. Cellular uptake of glucose is accomplished by means of binding to carrier proteins that increase its lipid solubility sufficiently to allow it to move through the cell membrane. Two classes of carriers have been described in animals—a sodium-glucose cotransporter and a facilitative glucose transporter.[8,9] The sodium-glucose cotransporter actively transports glucose across the cell membrane in conjunction with sodium. Sodium-glucose cotransport is involved in the uptake of glucose from the small intestine and the proximal tubule of the kidney.[10] Glucose uptake in other organs occurs by a saturable form of passive transport in which carrier proteins facilitate the diffusion of glucose across the cell membrane down its concentration gradient.

Five transporter isoforms encoded in DNA have been described; these isoforms are structurally related proteins that differentially regulate glucose uptake into various tissues.[8] Individual tissues and cells may express more than one transporter isoform. Three of the isoforms, GLUT1, GLUT2, and GLUT4, are thought to play important roles in glucose uptake. The GLUT1 isoform is responsible for basal glucose uptake; it can be found in many tissues. This isoform is present in highest concentration in the cells of blood-tissue barriers (eg, brain, placenta). It has a high affinity for glucose that ensures transport even under conditions of hypoglycemia. The GLUT2 isoform has a more restricted tissue distribution than GLUT1. It is expressed in the liver, kidney, small in-

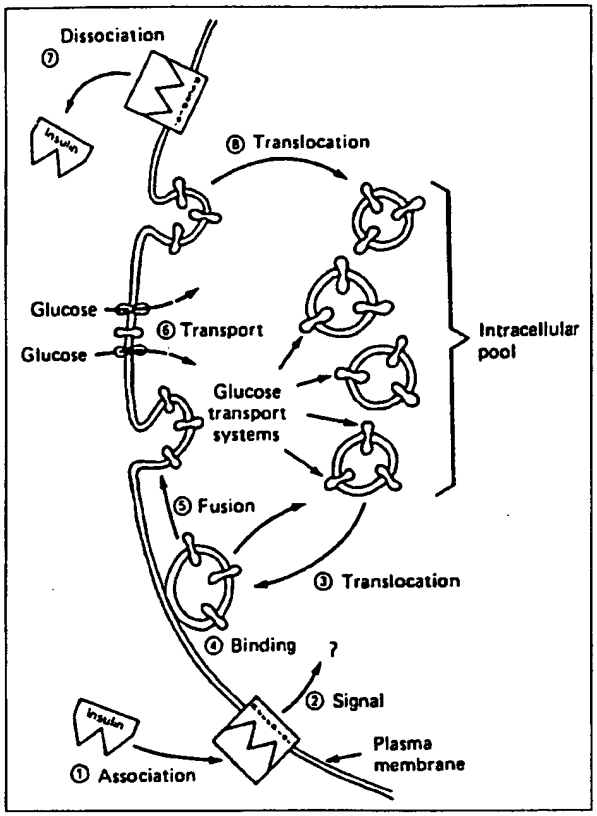

Figure 1. Translocation of glucose transporters by insulin. From Karnieli et al,[107] with permission.

testine, and pancreatic beta cells. In the liver, GLUT2 mediates the uptake and release of glucose by hepatocytes. In the pancreas, GLUT2 may be involved in the regulation of glucose-stimulated insulin secretion. Isoform GLUT4 is present only in tissues where glucose uptake is mediated by insulin (insulin-mediated glucose uptake, or IMGU), namely, muscle, fat, and heart tissue. Under basal conditions, GLUT4 is localized to intracellular vesicles with little in the plasma membrane, whereas GLUT1 is distributed equally between the plasma membrane and vesicles.[8]

Cushman and Wardzala[11] in 1980 described a molecular mechanism by which insulin could increase glucose uptake in adipocytes. (Skeletal muscle may share this mechanism.[8]) They postulated that binding of insulin to receptor sites on the cell membrane increases glucose uptake by stimulating the reversible migration of an intracellular pool of carrier proteins to the cell membrane (**Figure 1**). Insulin also promotes glucose uptake by increasing the intrinsic activity (V_{max}) of carrier proteins, although the mechanism by which this occurs is unclear.[9,11,12] Counterregulatory hormones such as catecholamines or glucagon may antagonize the action of insulin in muscle and fat by decreasing the intrinsic activity of the GLUT4 transporter isoform.[12,13]

Peripheral glucose uptake also occurs by noninsulin-mediated glucose uptake (NIMGU). This process transpires in the central nervous system, liver, leukocytes, and erythrocytes; it also occurs in insulin-sensitive tissues such as skeletal muscle and fat.[7,14] Under basal postabsorptive conditions, approximately 80% of whole body glucose uptake is by NIMGU (predominately by the central nervous system).[15] Skeletal muscle accounts for 20% of basal whole-body glucose uptake of which one half is NIMGU and one half IMGU. During conditions of hyperglycemia, peripheral glucose uptake exhibits a mass action effect in which uptake increases in direct proportion to the blood sugar.[14] Much of this increase is accounted for by augmented NIMGU in skeletal muscle.[14]

Increased whole-body glucose uptake during infection or following injury has several characteristics: It is largely noninsulin mediated, which suggests that the GLUT1 transporter may be the primary glucose carrier during stress[7,16]; it results from an enhanced rate of glucose utilization by tissues rich in macrophages such as spleen, ileum, liver, and lung[6,7]; it persists even during hypoglycemia[17]; and in contrast to the basal state, NIMGU in severe infection or injury is only minimally enhanced by hyperglycemia, possibly because stress increases glucose uptake to near maximal levels.[7]

Until recently, the stimulus for enhanced NIMGU during stress was unknown. Filkins[18] demonstrated in the late 1970s that supernatants obtained from peritoneal macrophages exposed to endotoxin increased glucose oxidation in a fat-pad assay system. They proposed the term "macrophage insulinlike activity" for the presumptive mediator. Lee et al[19] subsequently observed that tumor necrosis factor (TNF) increased hexose transport in muscle cells. TNF was also found to increase glucose uptake in dog hindlimb.[20] Meszaros et al[21] observed that administration of TNF increased glucose utilization in macrophage-rich tissues such as spleen, liver, and kidney, as well as in diaphragm tissue. Certain unidentified cytokines also appear to promote glucose uptake.[19] Widnell et al[22] and Pasternak et al[23] noted that BHK cells exposed to various forms of cellular stress increased glucose uptake as the consequence of an insulinlike reaction in which glucose transporters migrated from an intracellular site to the plasma membrane. Bird et al[24] noted that interleukin-1 stimulated hexose transport in fibroblasts by increasing the net rate of glucose transporter synthesis. Cornelius et al[25] found that monokines increased mRNA coding for synthesis of glucose transporter isoforms. Zeller et al[26] observed increased GLUT1 mRNA in fat, soleus muscle, and liver in a rat model of endotoxic shock; however, the significance of this

observation was unclear since in a subsequent study they found that membrane content of GLUT1 protein was not increased.[27] Stephens et al[16] were also unable to document increased membrane transporter protein despite increased GLUT1 mRNA.

In summary, stress is associated with an enhanced peripheral uptake of glucose. This process is largely noninsulin responsive, is most prominent in tissues involved in the immune response, and appears to be cytokine-mediated. It is likely that some alteration in synthesis, distribution, or intrinsic activity of the glucose transporter plays a role in this process. However, the mechanism by which stress enhances peripheral uptake of glucose requires further clarification.

ENHANCED PERIPHERAL GLUCOSE UTILIZATION

Once taken up by the cell, glucose is metabolized to pyruvate via glycolysis. Glucose may also be stored as glycogen. However, glycogen formation in liver and muscle appears to be inhibited during stress (see below). Patients resuscitated from severe injury or infection typically display augmented glycolysis; this has been attributed to a cellular energy deficit resulting from altered microcirculatory blood flow or mitochondrial dysfunction.[28,29] Recent advances in biotechnology have provided innovative methods to assess the status of tissue oxygenation and bioenergetics and have cast doubt on the concept of an ischemic or hypoxic stimulus for glycolysis. Techniques such as phosphorus 31 nuclear magnetic resonance spectroscopy and [^{18}F]-fluoromisonidazole have been used to explore the hypothesis that increased glycolysis during stress results from tissue hypoxia. Data obtained from muscle, heart, brain, and liver studies have failed to provide evidence of a depressed bioenergetic state during sepsis.[30-35] A detailed presentation of the data is beyond the scope of this review, and the reader is referred to a recent article for a more extensive discussion.[35]

It is likely that severe injury or infection provides a stimulus for glycolysis that is not mediated by tissue hypoxia. In the setting of stress, glycolytic activity is enhanced (via a mass action effect) by augmented cellular glucose uptake as well as by increased adenosine triphosphate (ATP) turnover and adenosine monophosphate (AMP) production, which stimulate phosphofructokinase, the rate-limiting enzyme of glycolysis.[35,36] Enhanced glycolytic activity in the presence of adequate tissue oxygenation (eg, aerobic glycolysis), has also been described in skeletal muscle during postprandial rest, during sustained submaximal exercise, and with administration of catecholamines.[37,38] Brain, renal medulla, gastrointestinal tract mucosa, retina, and leukocytes also normally metabolize glucose to lactate through aerobic glycolysis.[39]

Why certain types of cells choose to meet their energy requirements in this fashion is unclear. Augmented glycolysis may be necessary to sustain processes that require high rates of cytoplasmic ATP turnover.[38,40] An alternate interpretation, termed the "lactate shuttle," postulates that aerobic glycolysis confers increased metabolic flexibility by allowing different tissues to share a carbon source (lactate) for oxidation or gluconeogenesis.[38] Amaral et al[39] provided support for the shuttle hypothesis by demonstrating that lactate could substitute for glucose as an oxidative substrate in wounded tissue. Similarly, Spitzer et al[41] observed that endotoxemia promoted myocardial lactate oxidation. An increased local concentration of lactate may also contribute to tissue repair by inhibiting bacterial growth, increasing wound blood flow, and stimulating collagen synthesis by the fibroblast.[5]

Pyruvate produced by glycolysis may be directed into one of four pathways (**Figure 2**): (1) oxidation to carbon dioxide, (2) conversion to lactate, (3) transamination to alanine, and (4) recycling to glucose via oxaloacetate. Previous studies have suggested that oxidative metabolism of pyruvate is impaired following injury or infection.[42-44] However, these studies measured pyruvate oxidation indirectly utilizing a technique that incorporates radiolabeled glucose and exhaled gas analysis. This method may give falsely low values for oxidation because it fails to account for glucose-6-phosphate derived from glycogenolysis; that in turn could result in overestimation of the precursor (pyruvate) for oxidation.[36] Recently, Wolfe et al,[36] studying burn patients, utilized a stable isotope technique that allows direct quantification of pyruvate production and oxidation. They found an increase in the total rate of glucose oxidation in the basal state and during glucose infusion. This finding casts doubt on the concept of decreased glucose oxidation during stress.

In summary, stress is associated with an enhanced glycolytic and oxidative utilization of glucose that may be directed toward satisfying the increased metabolic demands of tissues involved in the reparative process.

HYPERLACTATEMIA

Persistant hyperlactatemia is not uncommon in patients who have been resuscitated from severe injury or infection.[3,36,45,46] This phenomenon is most apparent in patients with septic stress who may have blood lactate concentrations that approach 5 mm/L.[45] The mechanism for hyperlactatemia in this setting had been attributed to tissue hypoperfusion. However, as mentioned above, conclusive evidence for tissue hypoxia in resuscitated stress is lacking. In contrast to hypoperfused states in which lactate is disproportionately increased relative to pyruvate, hyperlac-

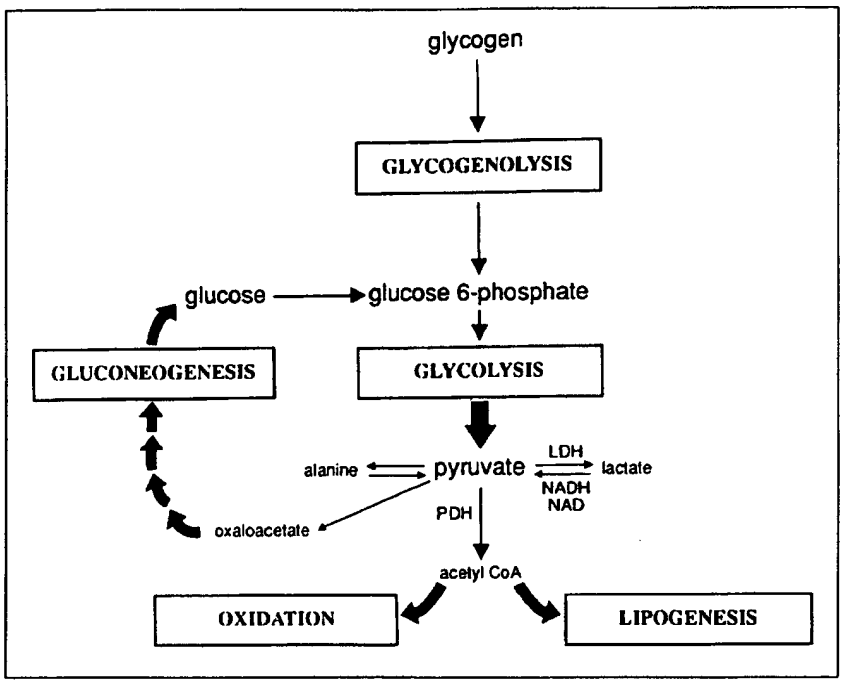

Figure 2. Overview of carbohydrate metabolism. PDH = pyruvate dehydrogenase; LDH = lactate dehydrogenase; NADH = reduced form of nicotinamide-adenine dinucleotide; NAD = nicotinamide-adenine dinucleotide.

tatemia of injury or infection (stress hyperlactatemia) is accompanied by elevations in pyruvate concentration that maintain the normal lactate/pyruvate ratio of 10:1 to 15:1.[3,45,47] That suggests that stress hyperlactatemia represents an equilibration phenomenon.[3,45] The degree of hyperlactatemia parallels the severity of hypermetabolism and is accompanied by concomitant increases in urinary nitrogen excretion, oxygen consumption, and insulin resistance (**Table**).[2] Stress hyperlactatemia is promoted by enhanced peripheral glucose uptake, which in turn stimulates production of lactate and pyruvate by a mass-action effect on glycolysis.[36,48] (Skeletal muscle, because of its large mass, is the major producer of lactate during stress.) Increased glycogenolysis (see below) also promotes lactate formation by increasing the proportion of glucose that is directed to lactate.[49]

Alterations in lactate utilization can also influence blood lactate concentration. The majority of lactate produced during stress is recycled to glucose in the Cori cycle, discussed below.[50,51] Oxidative utilization of lactate is regulated by the activity of the pyruvate dehydrogenase (PDH) enzyme complex. The properties of PDH have been recently reviewed.[52] Pyruvate dehydrogenase in skeletal muscle is subject to regulation by end-product (eg, NADH, acetyl-CoA) inhibition and by covalent modification by a protein kinase that catalyzes conversion of active PDH to inactive PDH.[52,53] The kinase is inhibited competitively with respect to ATP by ADP, and noncompetitively by pyruvate.

Siegel et al[45] noted that patients with sepsis had marked increases in blood levels of pyruvate and its equilibrium products lactate and alanine. This finding suggested an impairment in the utilization of pyruvate that the investigators attributed to inhibition of PDH.[45] Several animal studies supported this hypothesis. Vary et al[54] used a rat model to compare the effects of sepsis and sterile inflammation on PDH activity. They found that sepsis was associated with decreased activity of PDH in skeletal muscle and liver, whereas PDH downregulation was not seen with sterile inflammation. A potential mechanism for PDH downregulation was provided by a subsequent study demonstrating that sepsis, but not sterile inflammation, induces a stable factor in skeletal muscle mitochondria that increases PDH kinase activity.[55] In addition, administration of dichloroacetate (which inhibits the inactivating PDH kinase) to animals with sepsis-induced hyperlactatemia was noted to result in a reduction in blood lactate concentration.[54,56]

On the other hand, Lang et al[57] were unable to find downregulated PDH in septic rats. Wolfe et al,[36] using a tracer technique in burn patients, were unable to document a reduction in pyruvate oxidation as would be expected with downregulated PDH activity; they instead found a 300% increase in pyruvate oxidation relative to normal controls. PDH appears to be rate-limiting for the complete oxidation of glucose since dichoroacetate stimulates the percent of pyruvate oxidized, thereby reducing blood lactate concentration.[36] However, it is possible that the decrease in lactate induced by dichloroacetate may have resulted from feedback inhibition of glycolysis by oxidatively produced ATP.[36] Thus, the role of PDH in promoting hyperlactatemia in stress is unclear since pyruvate oxidation is not decreased.

TABLE

Stress Stratification by Metabolic Criteria

Stress Level	Urine Nitrogen (g/day)	Plasma* Lactate (mmol/L)	Plasma† Glucose (mg/dL)	Insulin Resistance	Oxygen Consumption (mL/min/m²)
Low	<10	<1.5	<150	No	<140
Mid	10–20	1.5–3.0	150–250	Some	140–180
High	>20	>3	>250	Yes	>180

Data adapted from Cerra,[2] used with permission.
*With a lactate/pyruvate ratio <20 mmol/L.
†In the absence of diabetes mellitus, pancreatitis, and steroid therapy.

Persistent hyperlactatemia following resuscitation from stress can therefore be viewed as a marker of enhanced aerobic glycolytic flux. Nevertheless, in the patient with injury or infection, the presence of blood lactate concentration greater than 5 mmol/L, concurrent metabolic acidosis, or lactate clearance with augmented oxygen delivery favors tissue hypoxia as the cause.[47] It should also be appreciated that normal blood lactate does not rule out tissue hypoperfusion since its concentration in blood largely reflects production relative to utilization. Regional tissue hypoperfusion can therefore coexist with normal blood lactate if local increases in lactate production are masked by efficient systemic clearance.[58]

INCREASED GLUCONEOGENESIS

Gluconeogenesis includes all pathways responsible for the conversion of noncarbohydrate substrates to glucose or glycogen. Gluconeogenesis is typically increased during stress and serves as a mechanism by which the availability of glucose is maintained.[50,59] Glucose recycling from lactate and alanine accounts for much of the increase in glucose production during stress.[50,51] Lactate released from skeletal muscle and other tissues is recycled to glucose in the Cori cycle whereas glucose is reconstituted from alanine in the glucose-alanine cycle (**Figure 3**).[60] The Cori cycle serves several purposes: It provides a continuous source of glucose for tissues that have an absolute requirement for glucose (eg, wound and other tissues involved in the immune response, brain, and erythrocytes); it conserves glucose carbons by preventing oxidative catabolism of glucose; and it buffers endogenous acid production.[47]

Alanine release from skeletal muscle is markedly increased during stress and exceeds its constitution in muscle; only 30% of alanine in blood is derived from skeletal muscle breakdown and the majority originates from de novo synthesis.[60-62] The carbon skeleton of this "new" alanine is derived from glucose-derived pyruvate whereas the ammonia moiety is provided by deamination of branched-chain amino acids.[63] Alanine also serves as a way of transporting ammonia to the liver in a nontoxic form. Glycerol is another important gluconeogenic substrate; it provides the major source of new carbons since, unlike lactate or alanine, it is not recycled.[5,64,65] Although the contribution of glycerol to glucose production in a normal fasted individual is minimal, fat mobilization induced by stress can increase its contribution to glucose production by as much as 20%.[66]

Hormones play an important role in regulating gluconeogenesis. Glucagon, cortisol, and epinephrine stimulate the process while insulin inhibits hepatic glucose production. Gluconeogenesis is also regulated by end-product inhibition in which hyperglycemia feeds back to directly decrease it independent of changes in hormonal levels. Enhanced gluconeogenesis during stress exhibits resistance to inhibition by insulin and glucose. It is likely that this resistance results from persistent gluconeogeneic stimulation by glucagon and other hormones.[67,68] It has also been postulated that increased peripheral production of gluconeogenic precursors (eg, lactate, alanine) could stimulate gluconeogenesis.[69]

In order to determine the origin of increased glucose-alanine cycling, Wolfe et al[70] measured the response of alanine flux to glucose infusion and vice versa in normal volunteers. They noted that alanine infusion did not stimulate glucose production whereas glucose infusion increased alanine flux by 35%. This observation implies that pyruvate availability is rate limiting for peripheral formation of alanine and is not rate limiting for gluconeogenesis. It is possible that inflammatory mediators may have a role in enhancing gluconeogenesis. Roh et al[71] found that hepatocytes from rats injected intraperitoneally with interleukin-1 increased alanine uptake and glucose production. However, hepatocytes from normal rats incubated with interleukin-1 failed to display these changes. This finding suggested that the effects of interleukin-1 on alanine uptake and gluconeogenesis were probably hormonally mediated.

Although stress is typically associated with increased gluconeogenesis, there is evidence that septic stress may be distinguished by a biphasic response; lethal models of sepsis in animals demonstrate an initial phase of hyperglycemia during

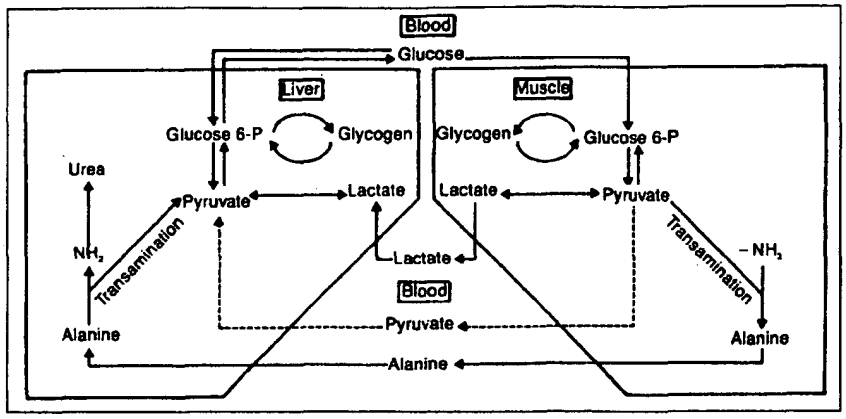

Figure 3. Lactic acid (Cori) and glucose-alanine cycles. Glucose 6-P = glucose 6-phosphate; $-NH_2$ = ammonia. From Mizock,[47] with permission.

which gluconeogenesis is increased, followed by a subsequent phase during which glucose production is suppressed and hypoglycemia occurs.[68,72] Wilmore et al[73] observed this biphasic response in burn patients who developed septic complications. Durkot and Wolfe[74] demonstrated that if adrenergic blockade is induced while glucagon and insulin levels are normalized, glucose production is decreased in sepsis whereas production is maintained in burn. Their finding implies that there is a factor inhibiting glucose production in sepsis that is not present in uncomplicated burn injury.

It has been observed that endotoxin-induced hypoglycemia in rats is associated with a decrease in activity of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme in gluconeogenesis.[75] Since PEPCK is not subject to allosteric regulation, the major determinant of its activity is expression of the gene coding for its synthesis.[76] Hill and McCallum[77] discovered that interleukin-6 decreased cyclic adenosine monophosphate (cAMP) induction of PEPCK gene expression, suggesting that inhibition of gluconeogenesis by inflammatory mediators may play a role in hypoglycemia associated with sepsis. Similarly, Deutschman et al[76] found that the induction of sepsis in rats was associated with a 66% reduction in levels of PEPCK mRNA and an attenuated response of PEPCK expression to stimulation by glucagon. The case of a patient with hypoglycemia secondary to fulminant meningococcemia who had extremely high blood levels of interleukin-6 was recently reported.[78] It is also possible that hypoglycemia could be promoted by decreased hepatic export of glucose as the result of downregulation of the GLUT2 isoform (which mediates bidirectional glucose transport in liver). Zeller et al[26] found a significant reduction in GLUT2 mRNA abundance in a rat model of septic shock with severe hypoglycemia, a finding that would be consistent with this hypothesis.

Increased peripheral utilization of glucose also plays a role in the pathogenesis of hypoglycemia; animal models of sepsis have manifest hypoglycemia despite increased hepatic glucose production.[68] Although hypoglycemia in animals is common, it is said to be rare in humans.[79] However, the incidence of hypoglycemia may be greater than suggested by early studies; Nouel et al[80] demonstrated hypoglycemia in 15 of 30 cirrhotic patients with septicemia. Malnutrition, renal failure, diabetes, and overwhelming bacteremia may also predispose to hypoglycemia.[81] Hypoglycemia during sepsis is associated with a high mortality.[79]

In summary, stress induces an increase in gluconeogenic activity that appears to be directed toward maintaining glucose delivery to wound and immune tissues. Prolonged septic stress is distinguished by a biphasic response in which an initial increase in gluconeogenic activity is followed by decreased glucose production that may be associated with hypoglycemia.

DEPRESSED GLYCOGENESIS

Glycogen synthesis in animals occurs in virtually all tissues but is most prominent in liver and skeletal muscle. Liver glycogen is concerned with maintenance of normoglycemia by exporting hexose units whereas muscle glycogen serves as a readily available source of hexose for glycolysis within muscle itself. Two metabolic pathways serve to replace depleted hepatic glycogen stores.[82] The direct pathway involves synthesis of glycogen from glucose taken up from the portal vein. In the indirect pathway, glucose is initially metabolized in the periphery to lactate or alanine with subsequent gluconeogenic conversion in the liver followed by glycogen synthesis.[83]

Several studies have documented depressed glycogenesis in sepsis or severe burn injury. Lang et al[84] found that rats infused with endotoxin had a decreased net rate of hepatic glycogen synthesis. Their data also suggested that gluconeogenically derived (ie, from the indirect pathway) glucose-6-phosphate was diverted from glycogen synthesis towards glucose output. Evidence of impaired glycogen synthe-

sis has also been found in patients with burn injury,[36] and acute infection.[85]

The mechanism by which glycogenesis is inhibited may involve a persistently high rate of glycogen breakdown induced by stress hormones such as epinephrine and glucagon.[36] Alternatively, depressed glycogenesis may result from the inhibition of glycogen synthesis as the consequence of decreased glycogen synthase activity.[84] Lee et al[19] demonstrated that TNF stimulated glycogen breakdown in muscle cells, thereby implicating cytokines as etiologic in this process. Decreased glycogenesis during stress may have evolved as a means to promote hepatic glucose production and maintain glucose availability for tissues that are obligate glucose consumers. It is also possible that decreased glycogen formation in skeletal muscle may play a role in the pathogenesis of stress-induced insulin resistance.[85]

GLUCOSE INTOLERANCE AND INSULIN RESISTANCE

Hyperglycemia is commonly seen in stressed patients during administration of parenteral nutrition or other glucose-containing solutions. Under normal conditions, the major regulatory mechanism for glycemic control during glucose infusion is the suppressive effect of glucose and insulin on gluconeogenesis.[86] During hyperglycemia or with exercise, skeletal muscle and adipose tissue play a prominent role in maintaining glycemic control. This occurs in part through an insulin-mediated increase in glucose uptake. However, stimulation of glucose uptake requires higher plasma insulin levels than needed to suppress production.[87,88] During glucose infusion, the pancreatic response may not acutely generate insulin levels that are high enough to increase peripheral uptake, resulting in a rise in the plasma glucose level.

In the setting of infection or injury, glucose uptake in wound and other organs involved in the immune response help maintain glycemic control since counterregulatory hormones (eg, catecholamines, cortisol) do not modulate NIMGU in these tissues. However, once uptake in these areas is saturated, hyperglycemia may occur due to defective suppression of gluconeogenesis and resistance to the peripheral action of insulin. Although skeletal muscle has traditionally been implicated as the major site of peripheral insulin resistance, stress may also induce insulin resistance in adipose tissue, liver, and heart.[89-92] Lang et al[93] attempted to determine the site of insulin resistance in a rat model of gram-negative sepsis and found that insulin resistance was most prominent in skeletal muscle of the hindlimb, whereas glucose uptake in abdominal muscle, diaphragm, heart, and epididymal fat was not impaired. It was concluded that decreased IMGU in muscle was the major cause of whole-body insulin resistance in sepsis; however, this defect may only involve certain muscle groups.

Peripheral insulin resistance may involve impaired insulin receptor binding or a postreceptor defect in glucose utilization, or both. In an attempt to ascertain the etiology of the defect, Shangraw et al[94] applied the physiology that insulin receptor binding in skeletal muscle stimulates both glucose and potassium uptake. They noted that septic patients with insulin resistance had elevated insulin-mediated plasma potassium clearance relative to controls. This finding implied that insulin binding to membrane receptors was intact, thereby supporting the hypothesis of a postreceptor mechanism for insulin resistance.

The precise mechanism for peripheral insulin resistance during stress is unknown. However, it is likely that the mechanism in some way involves the rate-limiting step for glucose disposal (ie, the process or metabolic step that ultimately determines the amount of glucose metabolized in tissue). Fink et al[95] provided evidence that, under normal conditions, glucose uptake is a saturable system in which glucose transport is rate-limiting for glucose uptake. Data that elucidate the rate-limiting step in the insulin-resistant state associated with stress are lacking. However, studies performed in other insulin-resistant states (notably diabetes) have provided some insight into the process. Yki-Jarvinen et al,[96] in a study of insulin-resistant type I diabetics, localized the rate-limiting defect for glucose disposal in skeletal muscle to the level of glucose transport. Kashiwagi et al[97] also found decreased insulin-stimulated glucose transport in insulin-resistant patients with type II diabetes.

Kuroda et al[13] observed that counterregulatory hormones such as catecholamines and glucagon decrease glucose uptake in the rat adipocyte by decreasing the intrinsic activity of the glucose transporter. It is possible, therefore, that the hormonal milieu associated with stress could induce insulin resistance by decreasing glucose transport. Alternatively, it has been observed that in certain settings, intracellular glucose metabolism becomes rate-limiting for glucose uptake. Kubo and Foley[98] noted that under hyperinsulinemic conditions, the rate-limiting step for IMGU and metabolism in muscle appears to shift from glucose transport to some step beyond transport. In insulin-resistant diabetes, a variety of posttransport defects in cellular metabolism have been identified, including alterations in glucose oxidation and muscle enzyme activities (eg, PDH, glycogen synthase).[99,100] Decreased glucose utilization in posttransport metabolic pathways could cause insulin resistance by promoting a rise in intracellular glucose concentration (which is normally close to zero); that in turn would inhibit further glucose up-

take by decreasing the intracellular/extracellular concentration gradient. It is possible that stress-induced depression of glycogenesis could cause insulin resistance by this mechanism. Several studies have dismissed the possibility of an intracellular defect as rate-limiting, based on their failure to demonstrate an increase in the concentration of free glucose in the intracellular space.[101,102] However, it has been suggested that the distribution of glucose may not be uniform throughout cellular water so that absence of an accumulation of free glucose does not rule out the possibility that defects in intracellular glucose metabolism are rate-limiting under certain conditions.[103]

In summary, stress-induced peripheral insulin resistance appears to be a postreceptor phenomenon. The precise mechanism underlying insulin resistance is unclear but could involve decreased glucose uptake in skeletal muscle as the consequence of inhibited glucose transport or as the result of an alteration in intracellular glucose metabolism.

IMPLICATIONS FOR NUTRITIONAL SUPPORT

An improved understanding of the pathogenic mechanisms underlying altered carbohydrate metabolism during stress should ideally translate into a more rational approach to the provision of nutritional support. Unfortunately, many of the observations outlined in the preceeding discussion are either preliminary or unproven in humans. Nevertheless, two specific areas of potential relevance should be emphasized. First, if one accepts the concept of hyperglycemia of injury or infection as beneficial by promoting cellular glucose uptake, then modest degrees of hyperglycemia should be tolerated without efforts to lower blood glucose to normal values of 90 to 120 mg/dL.[104] The level of glycemia should be high enough to maximize cellular glucose uptake without causing hyperosmolarity. A glucose concentration of 160 to 200 mg/dL has been recommended to achieve this goal and is probably acceptable to most clinicians.[105] Second, the necessity of providing a mixed caloric source (in which a percentage of the resting energy expenditure is provided as lipid calories) is brought into question since oxidative use of glucose appears to be unimpaired during critical illness.[36,85] The caloric mix oxidized during stress is determined largely by the relative availability of glucose, which is the preferred caloric substrate when given at rates below the resting energy expenditure.[106] Oxidation of fatty acids for energy occurs when glucose availability is limited.[106] However, there are several settings in which lipid administration is useful: as a more concentrated source of calories for patients who are volume restricted; for patients with glucose intolerance and insulin resistance; and for prolonged (eg, greater than 2 to 3 weeks) parenteral nutrition in order to prevent fatty acid deficiency.

CONCLUSION

Severe injury or infection is associated with alterations in carbohydrate metabolism that include enhanced glucose uptake and utilization, hyperlactatemia, increased glucose production, depressed glycogenesis, glucose intolerance, and insulin resistance. Teleologically, these changes may be viewed as providing a mechanism by which the energy demands of the wound and tissues active in the immune response are satisfied.

REFERENCES

1. Mordes JP, Rossini AA. Management of diabetes in the critically ill patient. In: Rippe JM, Irwin RS, Alpert JS, Dalen JE, eds. *Intensive Care Medicine*. Boston: Little, Brown; 1985:779–785.
2. Cerra FB. Multiple organ failure syndrome. In: Bihari DJ, Cerra FB, eds. *Multiple Organ Failure*. Fullerton, California: Society of Critical Care Medicine; 1989:1–24.
3. Cerra FB. Hypermetabolism, organ failure, and metabolic support. *Surgery*. 1987;101:1–14.
4. Stoner HB. Metabolism after trauma and in sepsis. *Circ Shock*. 1986;19:75–87.
5. Wilmore DW. The wound as an organ. In: Little RA, Frayn KN, eds. *The Scientific Basis for the Care of the Critically Ill*. Manchester, UK: Manchester University Press; 1986:45–59.
6. Meszaros K, Lang CH, Bagby GJ, Spitzer JJ. Contribution of different organs to increased glucose consumption after endotoxin administration. *J Biol Chem*. 1987;262:10965–10970.
7. Lang CH, Dobrescu C. Gram-negative infection increases noninsulin-mediated glucose disposal. *Endocrinology*. 1991;128:645–653.
8. Pessin JE, Bell G. Mammalian facilitative glucose transporter family: structure and molecular regulation. *Annu Rev Physiol*. 1992;54:911–930.
9. Baly DL, Horuk R. The biology and biochemistry of the glucose transporter. *Biochem Biophys Acta*. 1988; 947:571–590.
10. Bell GI, Kayano T, Buse JB, et al. Molecular biology of mammalian glucose transporters. *Diabetes Care*. 1990;13:198–208.
11. Cushman SV, Wardzala LJ. Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. *J Biol Chem*. 1980;255:4758–4762.
12. Simpson IA, Cushman SW. Hormonal regulation of mammalian glucose transport. *Annu Rev Biochem*. 1986;55:1059–1089.
13. Kuroda M, Honnor RC, Cushman SW, et al. Regulation of insulin-stimulated glucose transport in the isolated rat adipocyte. *J Biol Chem*. 1987;262: 245–253.
14. Baron AD, Brechtel G, Wallace P, Edelman SV. Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol*. 1988;255:E769–E774.
15. Huang SC, Phelps ME, Hoffman EJ, et al. Noninvasive determination of local cerebral metabolic rate of glucose in man. *Am J Physiol*. 1980; 238:E69–E82.
16. Stephens JM, Bagby GJ, Pekala PH, et al. Differential regulation of glucose transporter gene expression in adipose tissue of septic rats. *Biochem Biophys Res Com*. 1992;183:417–422.
17. Lang CH, Dobrescu C. Sepsis-induced increases in glucose uptake by macrophage-rich tissues persist during hypoglycemia. *Metabolism*. 1991;40:585–593.
18. Filkins JP. Insulin-like activity (ILA) of a macrophage mediator on adipose tissue glucose oxidation. *J Reticuloendothel Soc*. 1979;25:591–595.
19. Lee MD, Zentella A, Pekala PH, Cerami A. Effect of endotoxin-induced monokines on glucose metabolism in the muscle cell line L6. *Proc Natl Acad Sci USA*. 1987;84:2590–2594.

20. Evans DA, Jacobs DO, Wilmore DW. Tumor necrosis factor enhances glucose uptake by peripheral tissues. *Am J Physiol.* 1989;257:R1182–R1189.
21. Meszaros K, Lang CH, Bagby GJ, Spitzer JJ. Tumor necrosis factor increases in vivo glucose utilization of macrophage-rich tissues. *Biochem Biophys Res Com.* 1987;149:1–6.
22. Widnell CC, Baldwin SA, Davies A, et al. Cellular stress induces a redistribution of the glucose transporter. *FASEB J.* 1990;4:1634–1637.
23. Pasternak CA, Aiyathurai JEJ, Makinde V, et al. Regulation of glucose uptake by stressed cells. *J Cellular Physiol.* 1991;149:324–331.
24. Bird TA, Davies A, Baldwin SA, Saklatvala J. Interleukin-1 stimulates hexose transport in fibroblasts by increasing the expression of glucose transporters. *J Biol Chem.* 1990;265:13578–13583.
25. Cornelius P, Lee MD, Marlow M, Pekala PH. Monokine regulation of glucose transporter mRNA in L6 myotubes. *Biochem Biophys Res Com.* 1989;165:429–436.
26. Zeller WP, Sian WT, Sweet M, et al. Altered glucose transporter mRNA abundance in a rat model of endotoxic shock. *Biochem Biophys Res Com.* 1991;176:535–540.
27. Zeller WE, Goto M, Parker J, et al. Glucose transporters (GLUT1, 2, & 4) in fat, muscle, and liver in a rat model of endotoxic shock. *Biochem Biophys Res Com.* 1994;198:923–927.
28. Cain SM. Supply dependency of oxygen uptake in ARDS: myth or reality. *Am J Med Sci.* 1984;288;119–124.
29. Mela L, Bacalzo LV, Miller LD. Defective oxidative metabolism of rat mitochondria in hemorrhagic and endotoxin shock. *Am J Physiol.* 1971;220:571–577.
30. Hotchkiss RS, Rust RS, Dence CS, et al. Evaluation of the role of cellular hypoxia in sepsis by the hypoxic marker [^{18}F]fluoromisonidazole. *Am J Physiol.* 1991;261:R965–R972.
31. Jacobs DO, Kobayashi T, Imagire J, et al. Sepsis alters skeletal muscle energetics and membrane function. *Surgery.* 1991;110:318–326.
32. Song SK, Hotchkiss RS, Karl IE, Ackerman JJH. Concurrent quantification of tissue metabolism and blood flow via ^{8}H/^{31}P NMR in vivo. III. Alterations of muscle blood flow and metabolism during sepsis. *Magnetic Res Med.* 1992;25:67–77.
33. Hotchkiss RS, Song SK, Neil JJ, et al. Sepsis does not impair tricarboxylic acid cycle in the heart. *Am J Physiol.* 1991;260:C50–C57.
34. Hotchkiss RS, Long RC, Hall JR, et al. An in vivo examination of rat brain during sepsis with ^{31}P-NMR spectroscopy. *Am J Physiol.* 1989;257: C1055–C1061.
35. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *JAMA.* 1992;267:1503–1519.
36. Wolfe RR, Jahoor F, Herndon D, Miyoshi H. Isotopic evaluation of the metabolism of pyruvate and related substrates in normal adult volunteers and severely burned children: effect of dichloroacetate and glucose infusion. *Surgery.* 1991;110:54–67.
37. Cerra FB. The syndrome of hypermetabolism and multiple system organ failure. In: Hall JB, Schmidt GA, Wood LAD, eds. *Principles of Critical Care.* New York: McGraw Hill; 1992:656–666.
38. Brooks GA. Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise. *Fed Proc.* 1986;45:2924–2929.
39. Amaral JF, Shearer JD, Mastrofrancesco MS, et al. Can lactate be used as a fuel by wounded tissue? *Surgery.* 1986;100:252–261.
40. Cohen SR. Why does brain make lactate? *J Theoret Biol.* 1985;112:429–432.
41. Spitzer JJ, Bechtel AA, Archer LT, et al. Myocardial substrate utilization in dogs following endotoxin administration. *Am J Physiol.* 1974;227:132–136.
42. Clowes CHA Jr, O'Donnell TF, Blackburn GF, Maki TN. Energy metabolism and proteolysis in traumatized and septic man. *Surg Clin North Am.* 1976;56:1169–1184.
43. Wolfe RR, Durkot MJ, Allsop JR, Burke JF. Glucose metabolism in severely burned patients. *Metabolism.* 1979;28:1031–1039.
44. Stoner HB, Little RA, Frayn KN, et al. The effect of sepsis on the oxidation of carbohydrate and fat. *Br J Surg.* 1983;70:32–35.
45. Siegel JH, Cerra FB, Coleman B, et al. Physiological and metabolic correlations in human sepsis. *Surgery.* 1979;86:163–193.
46. Cerra FB, Siegel JH, Border J, Coleman B. Correlations between metabolic and cardiopulmonary measurement in patients after trauma, general surgery and sepsis. *J Trauma.* 1979:19:621–628.
47. Mizock BA. Lactic acidosis. *Dis Mon.* 1989;35:233–300.
48. Vary TC, Siegel JH, Tall BD, Morris JG. Metabolic effects of partial reversal of pyruvate dehydrogenase activity by dichloroacetate in sepsis. *Circ Shock.* 1988;24:3–18.
49. Bagby GJ, Lang CH, Hargrove DM, et al. Glucose kinetics in rats infused with endotoxin-induced monokines or tumor necrosis factor. *Circ Shock.* 1988;24:111–121.
50. Wolfe RR, Burke JF. Effect of glucose infusion on glucose and lactate metabolism in normal and burned guinea pigs. *J Trauma.* 1978;18:800–805.
51. Long CL, Spencer JL, Kinney JM, Geiger JW. Carbohydrate metabolism in man: effect of elective operations and major injury. *J Appl Physiol.* 1971;31: 110–116.
52. Behal RH, Buxton DB, Robertson JG, Olson MS. Regulation of the pyruvate dehydrogenase multienzyme complex. *Ann Rev Nutr.* 1993;13:497–520.
53. Randle PJ. Fuel selection in animals. *Biochem Soc Trans.* 1986;14: 799–806.
54. Vary TC, Siegel JH, Nakatani T, et al. Regulation of glucose metabolism by altered pyruvate dehydrogenase activity. I. Potential site of insulin resistance in sepsis. *JPEN J Parenter Enternal Nutr* 1986;10:351–355.
55. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. *Am J Physiol.* 1991;260:E669–E674.
56. Vary TC, Siegel JH, Zechnich A, et al. Pharmacological reversal of abnormal glucose regulation, BCAA utilization, and muscle catabolism in sepsis by dichloroacetate. *J Trauma.* 1988;28:1301–1311.
57. Lang CH, Bagby GJ, Blakesley HL, Spitzer JJ. Glucose kinetics and pyruvate dehydrogenase activity in septic rats treated with dichloroacetate. *Circ Shock.* 1987;23:131–141.
58. Kruse JA, Carlson RW. Lactate metabolism. *Crit Care Clin.* 1987;3:725–746.
59. Gump FE, Long CL, Geiger JW, Kinney JM. The significance of altered gluconeogenesis in surgical catabolism. *J Trauma.* 1975;15:704–713.
60. Felig P. The glucose-alanine cycle. *Metabolism.* 1973;22:179–207.
61. Chang TW, Goldberg AL. The origin of alanine produced in skeletal muscle. *J Biol Chem.* 1978;253:3677–3684.
62. Felig P, Pozefsky T, Marliss E, Cahill GF Jr. Alanine: key role in gluconeogenesis. *Science.* 1970;167:1003–1004.
63. Haymond MW, Miles JM. Branched chain amino acids as a major source of alanine nitrogen in man. *Diabetes.* 1982;31:86–89.
64. Bortz WM, Paul P, Haff AC, Holmes WL. Glycerol turnover and oxidation in man. *J Clin Invest.* 1972;51:1537–1546.
65. Boija PO, Nulander G, Ware J. The effect of hemorrhagic stress on liver gluconeogenesis. *Acta Chir Scand.* 1987;153:273–278.
66. Wolfe RR. Carbohydrate metabolism in the critically ill patient. *Crit Care Clinics.* 1987;3:11–24.
67. Wolfe RR, Burke JF. Somatostatin infusion inhibits glucose production in burn patients. *Circ Shock.* 1982;9:521–527.
68. Wolfe RR, Burke JF. Glucose and lactate metabolism in experimental septic shock. *Am J Physiol.* 1978;235:R219–R227.
69. Spitzer JJ, Bagby GJ, Meszaros K, Lang CH. Alterations in lipid and carbohydrate metabolism in sepsis. *JPEN J Parenter Enternal Nutr.* 1988;12: 53S–58S.
70. Wolfe RR, Jahoor F, Herndon DN, Wolfe MH. The glucose-alanine cycle: origin of control. *JPEN J Parenter Enternal Nutr.* 1985;9:107. Abstract.
71. Roh MS, Moldawer LL, Ekman LG, et al. Stimulatory effect of interleukin-1 upon hepatic metabolism. *Metabolism.* 1986;35:419–424.
72. Yelich MR, Witek-Janusek L, Filkins JP. Glucose dyshomeostasis in endotoxicosis: direct versus monokine-mediated mechanisms of endotoxin action. In: Szentivanyi A, Friedman H, Nowotny A, eds. *Immunobiology and Immunopharmacology of Bacterial Endotoxins.* New York: Plenum Press; 1986:111–132.
73. Wilmore DW, Goodwin CW, Aulick LH, et al. Effect of injury and infection on visceral metabolism and circulation. *Ann Surg.* 1980;192:491–504.
74. Durkot MJ, Wolfe RR. Effects of adrenergic blockade on glucose kinetics in septic and burned guinea pigs. *Am J Physiol.* 1981;241:R222–R227.
75. McCallum RE. Hepatocyte-Kupffer cell interactions in the inhibition of hepatic gluconeogenesis by bacterial endotoxin. In: Majde JA, Person RJ, eds. *Pathophysiological Effects of Endotoxins at the Cellular Level.* New York: Alan R. Liss; 1981:99–113.

76. Deutschman CS, DeMaio A, Buchman TG, Clemens MG. Sepsis-induced alterations in phosphoenolpyruvate carboxykinase expression: the role of insulin and glucagon. *Circ Shock.* 1993;40:295–302.
77. Hill M, McCallum R. Altered transcriptional regulation of phosphoenolpyruvate carboxykinase in rats following endotoxin treatment. *J Clin Invest.* 1991;88:811–816.
78. Romijn JA, Godfried MH, Wortel C, Sauerwein HP. Hypoglycemia, hormones and cytokines in fatal meningococcal septicemia. *J Endocrinol Invest.* 1990;13:743–747.
79. Miller SI, Wallace RJ Jr, Muscher DM, et al. Hypoglycemia as a manifestation of sepsis. *Am J Med.* 1980;68:649–654.
80. Nouel O, Bernuau J, Rueff B, Benhamou JP. Hypoglycemia: a common complication of septicemia in cirrhosis. *Arch Intern Med.* 1981;141: 1477–1478.
81. Scheetz A. Hypoglycemia and sepsis in two elderly diabetics. *J Am Geriatric Soc.* 1990;38:492. Letter.
82. Newgard CB, Hirsch LJ, Foster DW, McGarry JD. Studies on the mechanism by which exogenous glucose is converted into liver glycogen in the rat. *J Biol Chem.* 1983;258:8046–8052.
83. Shikama H, Ui M. Glucose load diverts hepatic gluconeogenic product from glucose to glycogen in vivo. *Am J Physiol.* 1978;235:E354–E360.
84. Lang CH, Bagby GJ, Buday AZ, Spitzer JJ. The contribution of gluconeogenesis to glycogen repletion during glucose infusion in endotoxemia. *Metabolism.* 1987;36:180–187.
85. Virkamaki A, Puhakainen I, Koivisto VA, et al. Mechanisms of hepatic and peripheral insulin resistance during acute infections in humans. *J Clin Endo Met.* 1992;74:673–679.
86. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: response to intravenous glucose infusion. *Metabolism.* 1979;28:210–220.
87. Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. *Am J Physiol.* 1981;240:E630–E639.
88. Kolterman OG, Insel J, Sackow M, Olefsky JM. Mechanisms of insulin resistance in human obesity. *J Clin Invest.* 1980;65:1272–1284.
89. Clemens MG, Chaudry IH, Daigneau N, Baue AE. Insulin resistance and depressed gluconeogenic capability during early hyperdynamic sepsis. *J Trauma.* 1984;24:701–708.
90. Holley DC, Spitzer JA: Insulin action and binding in adipocytes exposed to endotoxin in vitro and in vivo. *Circ Shock.* 1980;7:3–12.
91. Raymond RM, McLane MP, Law WR, et al. Myocardial insulin resistance during acute endotoxin shock in dogs. *Diabetes.* 1988;37:1684–1688.
92. Igarashi M, Yamatani K, Fukase N, et al. Sepsis inhibits insulin-stimulated glucose transport in isolated rat adipocytes. *Diabetes Res Clin Pract.* 1992;15:213–218.
93. Lang CH, Dobrescu C, Meszaros. Insulin-mediated glucose uptake by individual tissues during sepsis. *Metabolism.* 1990;39:1096–1107.
94. Shangraw RE, Jahoor F, Miyoshi H, et al. Differentiation between septic and postburn insulin resistance. *Metabolism.* 1989;38:983–989.
95. Fink RI, Wallace P, Brechtel G, Olefsky JM. Evidence that glucose transport is rate-limiting for in vivo glucose uptake. *Metabolism.* 1992;41:897–902.
96. Yki-Jarvinen H, Sahlin K, Ren JM, Koivisto VA. Localization of rate-limiting defect for glucose disposal in skeletal muscle of insulin-resistant type I diabetic patients. *Diabetes.* 1990;39:157–167.
97. Kashiwagi A, Verso MA, Andrews J, et al. In vitro insulin resistance of human adipocytes isolated from subjects with noninsulin-dependent diabetes mellitus. *J Clin Invest.* 1983;72:1246–1252.
98. Kubo K, Foley JE. Rate-limiting steps for insulin-mediated glucose uptake into perfused rat hindlimb. *Am J Physiol.* 1986;250:E100–E102.
99. Beck-Nielsen H, Wright K, Verity L, et al. Reduced glucose oxidation and pyruvate-dehydrogenase activity (PDH) in type I diabetics (insulin-dependent) in poor control. *Diabetes.* 1987;36(suppl1):30. Abstract.
100. Bogardus C, Lillioja S, Stone K, Mott D. Correlation between muscle glycogen synthase activity and in vivo insulin action in man. *J Clin Invest.* 1984;73:1185–1190.
101. Miller WJ, Sherman WM, Dodd H, Ivy JL. Influence of dietary carbohydrate on skeletal muscle glucose uptake. *Am J Clin Nut.* 1985;41:526–532.
102. Richter EA, Garetto LP, Goodman MN, Ruderman NB. Muscle glucose metabolism following exercise in the rat. *J Clin Invest.* 1982;69:785–793.
103. Foley JE, Cushman SW, Salans LB. Intracellular glucose concentration in small and large rat adipose cells. *Am J Physiol.* 1980;238:E180–E185.
104. Bursztein S, Elwyn DH, Askanazi J, Kinney JM. *Energy Metabolism, Indirect Calorimetry, and Nutrition.* Baltimore: WB Saunders; 1989:119–171.
105. Moore RS, Cerra FB. Sepsis. In: Fischer JE, ed. *Total Parenteral Nutrition.* 2nd ed. Boston: Little, Brown; 1991:347–365.
106. Wolfe RR. Metabolic response to burn injury: nutritional implications. *Semin Nephrol.* 1993;13:382–390.
107. Kamieli E, Zarnowski MJ, Hissin PJ, et al. Insulin-stimulated translocation of glucose transport systems in the isolated rat adipose cell. *J Biol Chem.* 1981;256:4772–4777.